Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Gaithersburg, Maryland
July 15, 2010

QNEXA (Phentermine/Topiramate) NDA 22580

Mary Dunne Roberts, MD
Division of Metabolism and Endocrinology Products

Outline

- Efficacy findings
- Safety concerns
  - Psychiatric adverse events
  - Neurocognitive adverse events
  - Cardiovascular safety
  - Metabolic acidosis
  - Teratogenicity

FDA 2007 Draft Guidance for Developing Products for Weight-Management: Fixed-dose combination

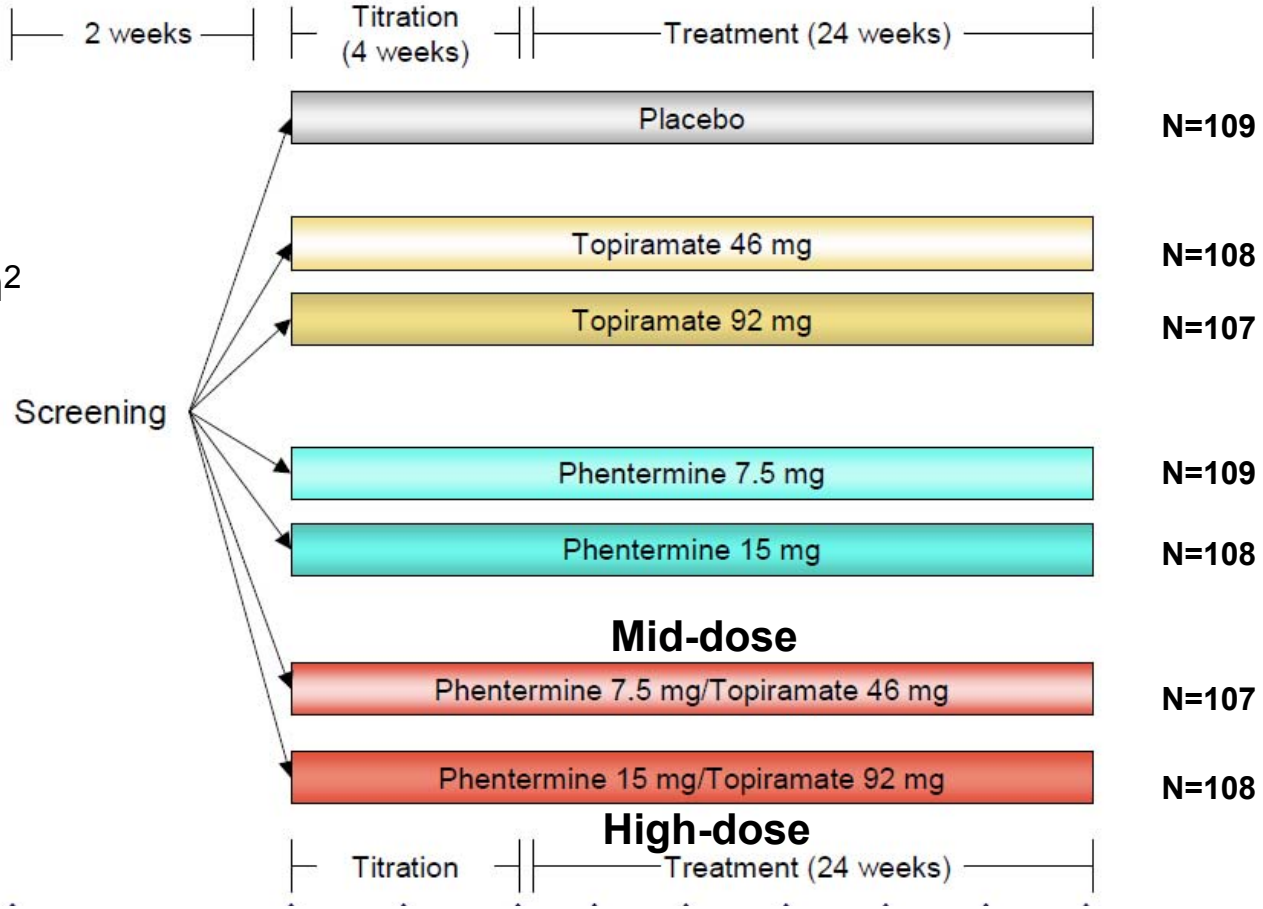
- Fixed-dose combination compared to components for efficacy and safety
- No minimum difference defined

Source: 2007 FDA Guidance

Study OB-301

Adults BMI ≥30 kg/m^2 and ≤45 kg/m^2

Type 2 diabetes excluded



Percent weight loss at Week 28 (ITT-LOCF): Study OB-301

Combination	LS Mean % loss	Comparator	LS Mean % loss	LS Mean % diff (95% CI)	p-value
Mid-dose PHEN/TPM (7.5/46 mg) versus	8.5	PHEN 7.5	5.5	3.0 (1.4, 4.6)	0.0003
		TPM 46	5.1	3.3 (1.7, 5.0)	<0.0001
High-dose PHEN/TPM (15/92 mg) versus	9.2	PHEN 15	6.1	3.2 (1.5, 4.8)	0.0001
		TPM 92	6.4	2.8 (1.1, 4.4)	0.0009

FDA 2007 Draft Guidance for Developing Products for Weight-Management: Fixed-dose combination

- Fixed-dose combination compared to components for efficacy and safety
- No minimum difference defined

Study OB-301 satisfied fixed-dose combination guidance

Source: 2007 FDA Guidance

FDA 2007 Guidance for Weight-loss Efficacy

- The drug's effect is significantly greater than that of placebo with the mean drug-associated weight loss exceeding mean placebo weight loss by at least 5%

OR

- The proportion of individuals on drug who lose at least 5% of their initial body weight is at least 35%, double the proportion and significantly greater than in those on placebo

Source: 2007 FDA Guidance

Study OB-302

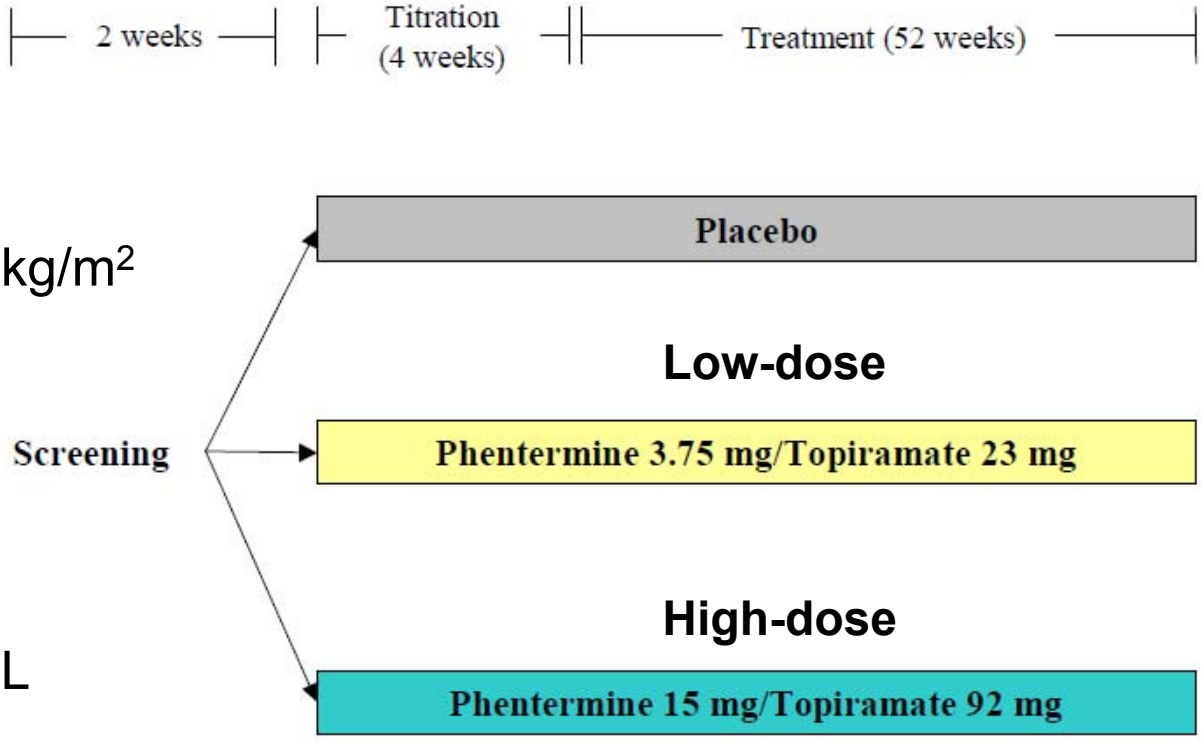
- Adults BMI ≥35 kg/m^2
- TG ≤200 mg/dL

(up to 1 lipid med)

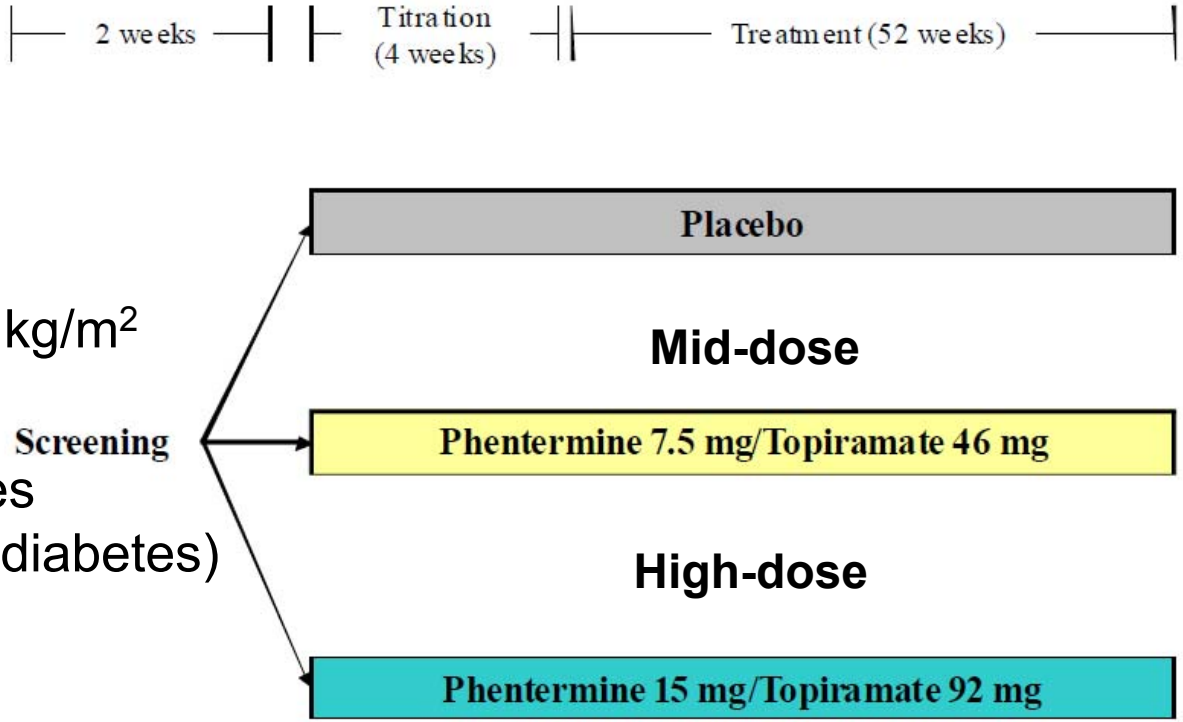
- BP≤140/90

(up to 2 HTN meds)

- FSG ≤110 mg/dL



Study OB-303

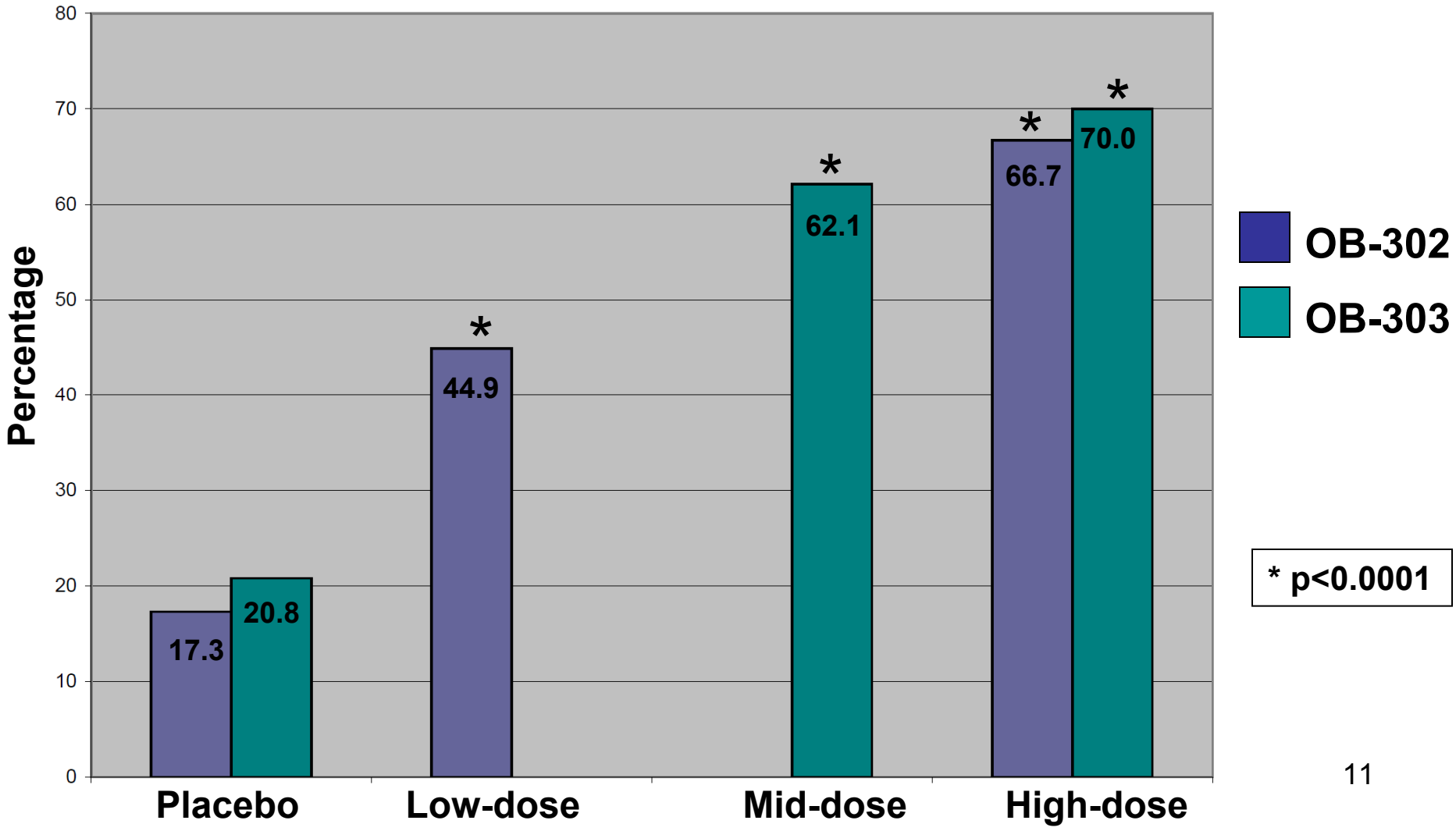


- Adults BMI ≥27 kg/m^2 and ≤45 kg/m^2
- 2+ co-morbidities (included type 2 diabetes)

Percent weight loss Week 56 (ITT-LOCF)

	Treatment group	Baseline mean wt (kg)	LS Mean % wt loss from baseline	LS Mean diff (95% CI)	p-value
OB-302	Placebo	116	1.6	--	--
	Low-dose PHEN/TPM	119	5.1	3.5 (2.4, 4.7)	<0.0001
	High-dose PHEN/TPM	115	10.9	9.4 (8.4, 10.3	<0.0001
OB-303	Placebo	103	1.2	--	--
	Mid-dose PHEN/TPM	103	7.8	6.6 (5.8, 7.4)	<0.0001
	High-dose PHEN/TPM	103	9.8	8.6 (8.0, 9.3)	<0.0001

Proportion with ≥5% weight loss at Week 56
(ITT-LOCF)



FDA 2007 Guidance for Weight-loss Efficacy

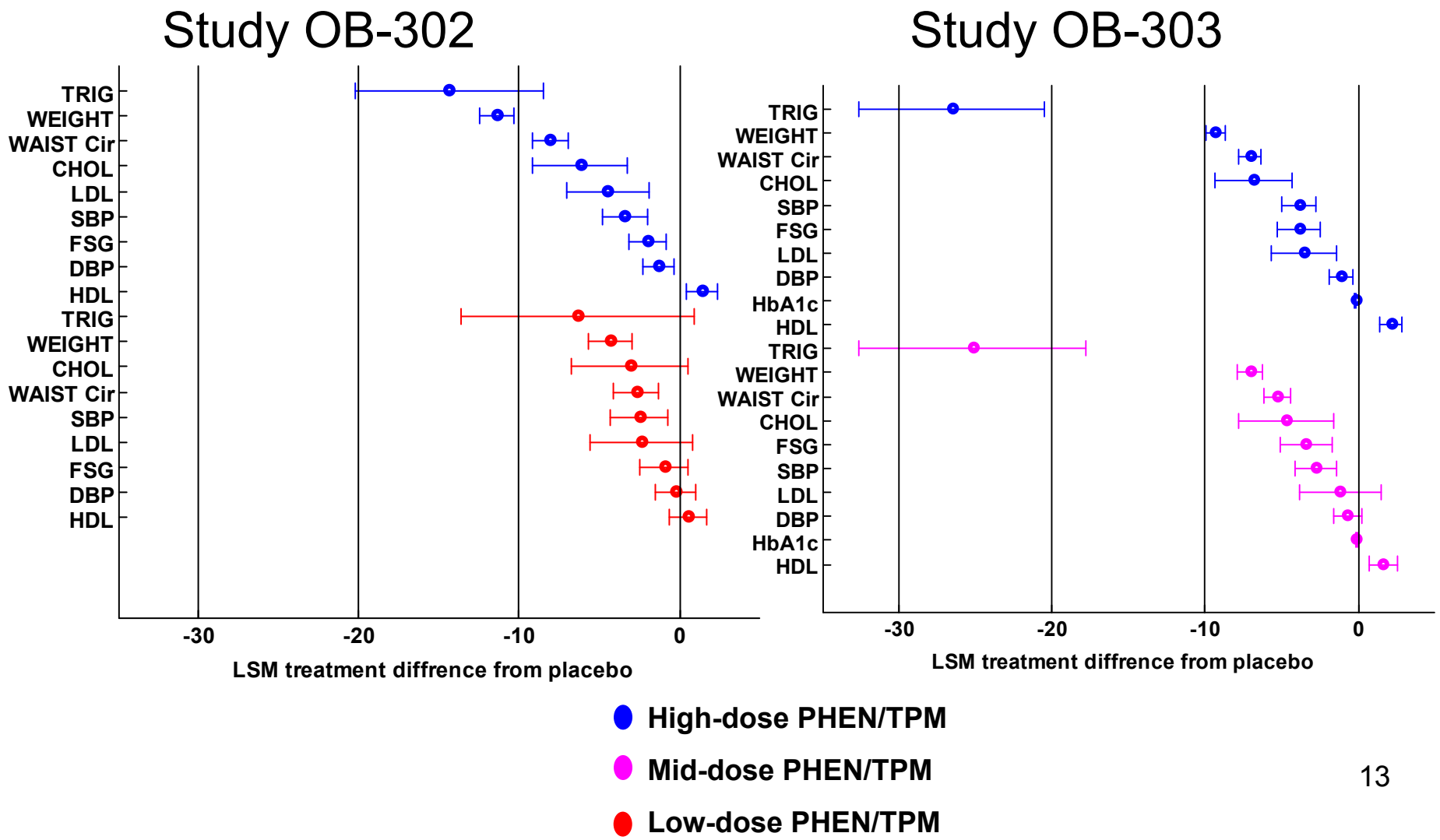
- The drug's effect is significantly greater than that of placebo with the mean drug-associated weight loss exceeding mean placebo weight loss by at least 5%

OR

- The proportion of individuals on drug who lose at least 5% of their initial body weight is at least 35%, double the proportion and significantly greater than in those on placebo

Study OB-302 and OB-303 met FDA 1-year efficacy benchmarks

Secondary and other endpoints



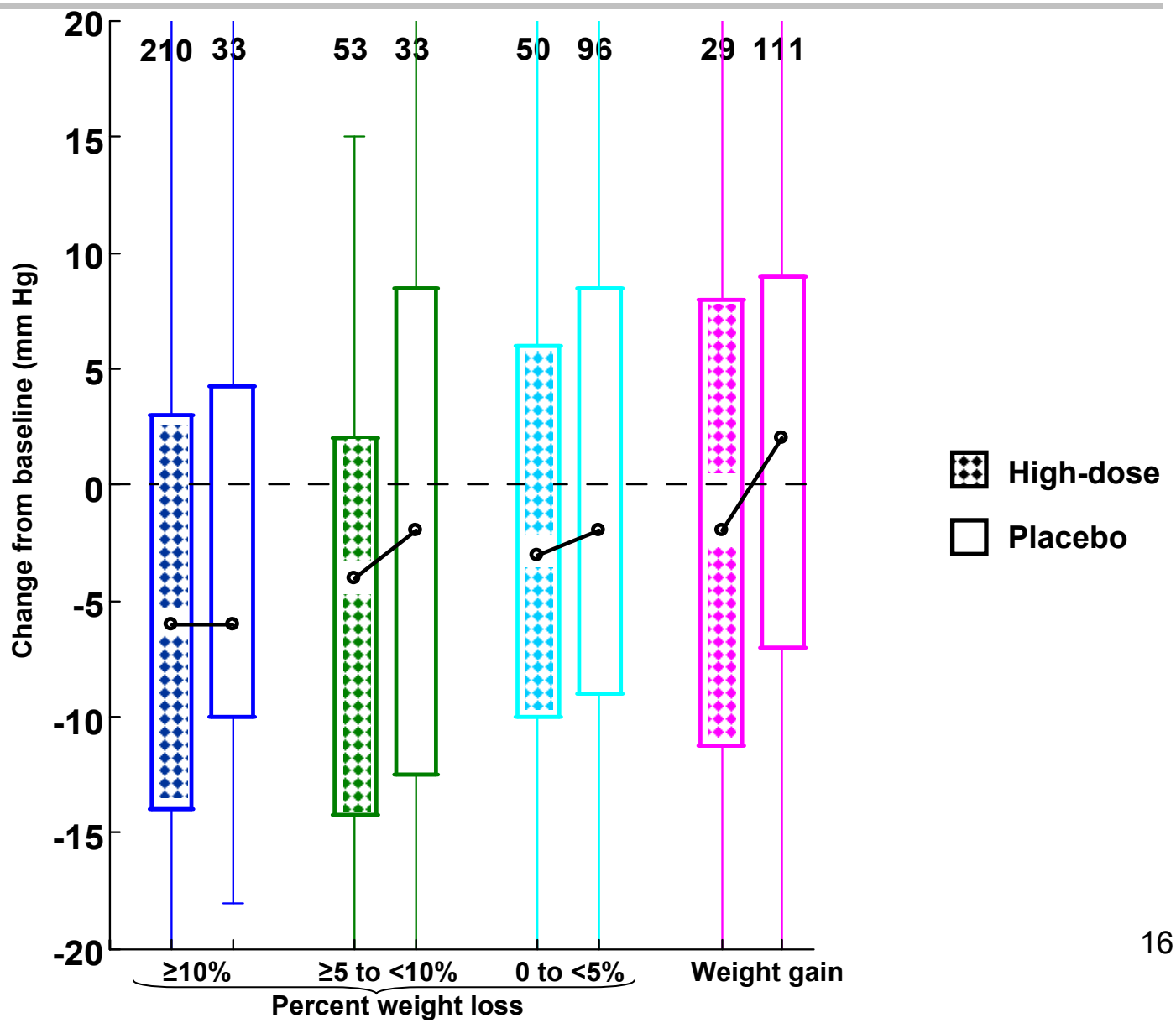
Weight-related co-morbidities: OB-302

	Low-dose treatment difference from placebo	p-value	High-dose treatment difference from placebo	p-value
Waist circumference	-2.5 cm	0.0006	-7.8 cm	<0.0001
Systolic blood pressure	-2.8 mmHg	0.0019	-3.8 mmHg	<0.0001
Diastolic blood pressure	-0.5 mmHg	NS	-1.9 mmHg	0.0002
LDL-C	-2.2%	NS	-2.8%	0.0157
HDL-C	0.5%	NS	3.5%	0.0005
Triglycerides	-3.9%	NS	-14.3%	<0.0001
Fasting serum glucose	-1.2 mg/dL	NS	-2.5 mg/dL	<0.0001
Framingham score	-0.2	NS	-0.3	0.0176

Weight-related co-morbidities: OB-303

	Mid-dose treatment difference from placebo	p-value	High-dose treatment difference from placebo	p-value
Waist circumference	-5.2 cm	<0.0001	-6.8 cm	<0.0001
Systolic blood pressure	-2.3 mmHg	0.0008	-3.2 mmHg	<0.0001
Diastolic blood pressure	-0.7 mmHg	NS	-1.1 mmHg	0.0031
LDL-C	0.4%	NS	-2.8%	0.0069
HDL-C	4.0%	<0.0001	5.6%	<0.0001
Triglycerides	-13.3%	<0.0001	-15.3%	<0.0001
HbA1c	-0.1%	<0.0001	-0.1%	<0.0001
Framingham score	-0.5	0.0052	-0.7	<0.0001

Systolic blood pressure



Efficacy conclusions

- PHEN/TPM achieved significantly greater weight loss compared to its components
- Low-, mid-, and high-dose PHEN/TPM achieved significantly greater mean percent weight loss and proportion of individuals achieving 5% weight loss compared to placebo
- PHEN/TPM associated weight loss was accompanied by small improvements in waist circumference, blood pressure, lipids, and HbA1c
- Impact on PHEN/TPM treatment on long-term cardiovascular outcomes unknown

Outline

- Efficacy findings
- Safety concerns
  - Psychiatric adverse events
  - Neurocognitive adverse events
  - Cardiovascular safety
  - Metabolic acidosis
  - Teratogenicity

Integrated summary of safety

- 6-month cohort
  - OB-202
  - OB-301
  - OB-302 (first 6 months)
  - OB-303 (first 6 months)
- 1-year cohort
  - OB-302
  - OB-303
  - OB202/DM230

PHEN/TPM exposure: 1-year safety cohort

- Number of individuals (adjusted for drug holidays)
  - Low-dose PHEN/TPM [mean (SD) 279 (147) days]
    - ≤ 1 month: 18
    - >1 to ≤6 months: 55
    - > 6 to ≤12 months: 30
    - > 12 months: 137
  - Mid-dose PHEN/TPM [mean (SD) 305 (142) days]
    - ≤ 1 month: 41
    - >1 to ≤6 months: 69
    - > 6 to ≤ 12 months: 53
    - > 12 months: 335
  - High-dose PHEN/TPM [mean (SD) 294 (175) days]
    - ≤ 1 month: 158
    - >1 to ≤ 6 months: 236
    - >6 to ≤ 12 months: 193
    - > 12 months: 993

Psychiatric adverse events

Phentermine and topiramate: psychiatric disorders

- Case reports of phentermine and psychosis at doses of 30 mg/day to 180 mg/day
  - Hoffman 1977, Devan 1990, Lee et al. 1998
- 24% of 431 patients with epilepsy reported adverse psychiatric effects after topiramate initiation
  - Affective (11%), psychotic (4%) disorders most frequent
  - Family and personal history, history of febrile seizures associated with psychiatric symptoms with topiramate
    - Mula et al. 2003
- Previous history of depression and rapid titration increases risk of depression with topiramate
  - Kanner et al. 2003, Mula et al. 2009

Relevant exclusion criteria

- Any history of bipolar disorder or psychosis
- More than one lifetime episode of major depression
- Current depression of moderate or greater severity (PHQ-9 score ≥10)
- Presence or history of suicidal behavior or ideation with some intent to act on it
- Antidepressant use that had not been stable for at least 3 months

6,703 screened for studies in 1-year safety cohort
276 (4.1%) failed due to the depression exclusion criteria

Baseline history of depression or taking anti-depressants

	Placebo N=1561 n (%)	Low-dose PHEN/TPM N=240 n (%)	Mid-dose PHEN/TPM N=498 n (%)	High-dose PHEN/TPM N=1580 n (%)
Depression h/o and/or on anti-depressants	**334 (21.4)**	**57 (23.8)**	**105 (21.1)**	**306 (19.4)**
-Depression history	192 (12.3)	33 (13.8)	58 (11.6)	271 (11.7)
-On anti-depressants	241 (15.4)	36 (15.0)	83 (16.7)	213 (13.5)

- Overall, 20.7% with history of depression or on anti-depressants at baseline in 1-year safety cohort

Patient Health Questionnaire-9

- PHQ-9 depression scale composed of nine items based on the nine criteria on which diagnosis of depressive disorders is based in DSM-IV

PHQ-9 sample

More than half the days

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	(2)	3
2	Feeling down, depressed, or hopeless	0	(1)	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	(2)	3
4	Feeling tired or having little energy	0	1	2	(3)
5	Poor appetite or overeating	0	(1)	2	3
6	Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	(2)	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	(2)	3
8	Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	(2)	3
9	Thoughts that you would be better off dead, or of hurting yourself in some way	(0)	1	2	3
	add columns:		+	+	
	TOTAL:				

Question 9: Thoughts that you would be better off dead, or of hurting yourself in some way

PHQ-9 questionnaire

- Total PHQ-9 score range 0 to 27
  - 0-4 “None”
  - 5-9 “Mild”
  - 10-14 “Moderate”
  - 15-19 “Moderately severe”
  - 20-27 “Severe”

- Score of 10 screening cutpoint for major depression

PHQ-9 results

- 74.4% of individuals at baseline no depression by PHQ-9

- No numerical imbalances throughout study
  - Elevated PHQ-9 score of ≥10
  - Worsening PHQ-9 score
  - Positive response to Question 9

PHQ-9 results

- PHQ-9 scores of individuals discontinuing due a depression related event were slightly higher on average than individuals who did not discontinue
- However, there were several instances of discontinuation with a PHQ-9 score of zero

	Discontinued due to depression-related AE	
	Yes	No
Mean PHQ-9 score	6.2	4.7

Targeted medical events

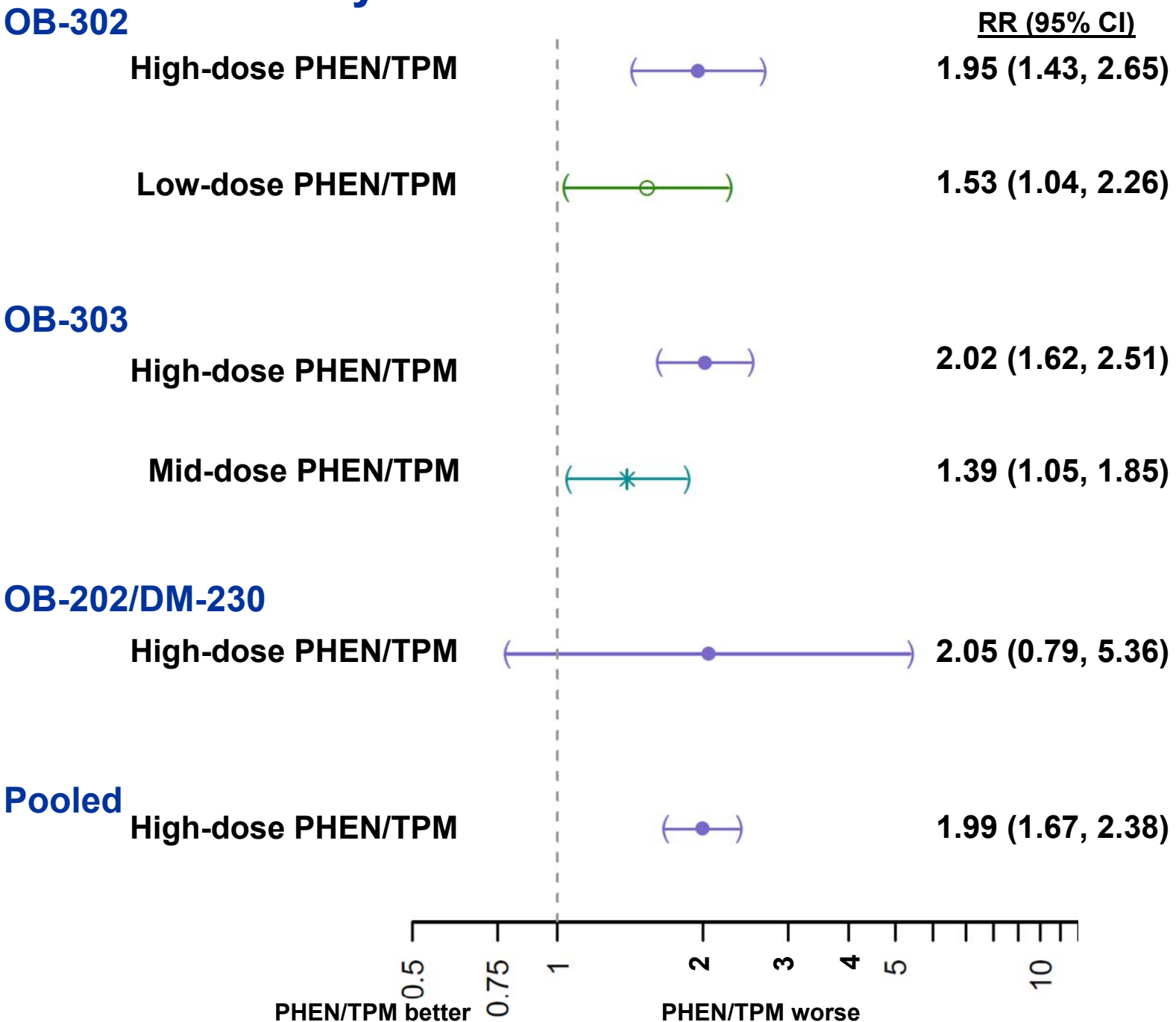
- **Psychiatric disorders**
  - Sleep disorders
  - Anxiety
  - Depression
  - Suicide/self-injury

Psychiatric disorders

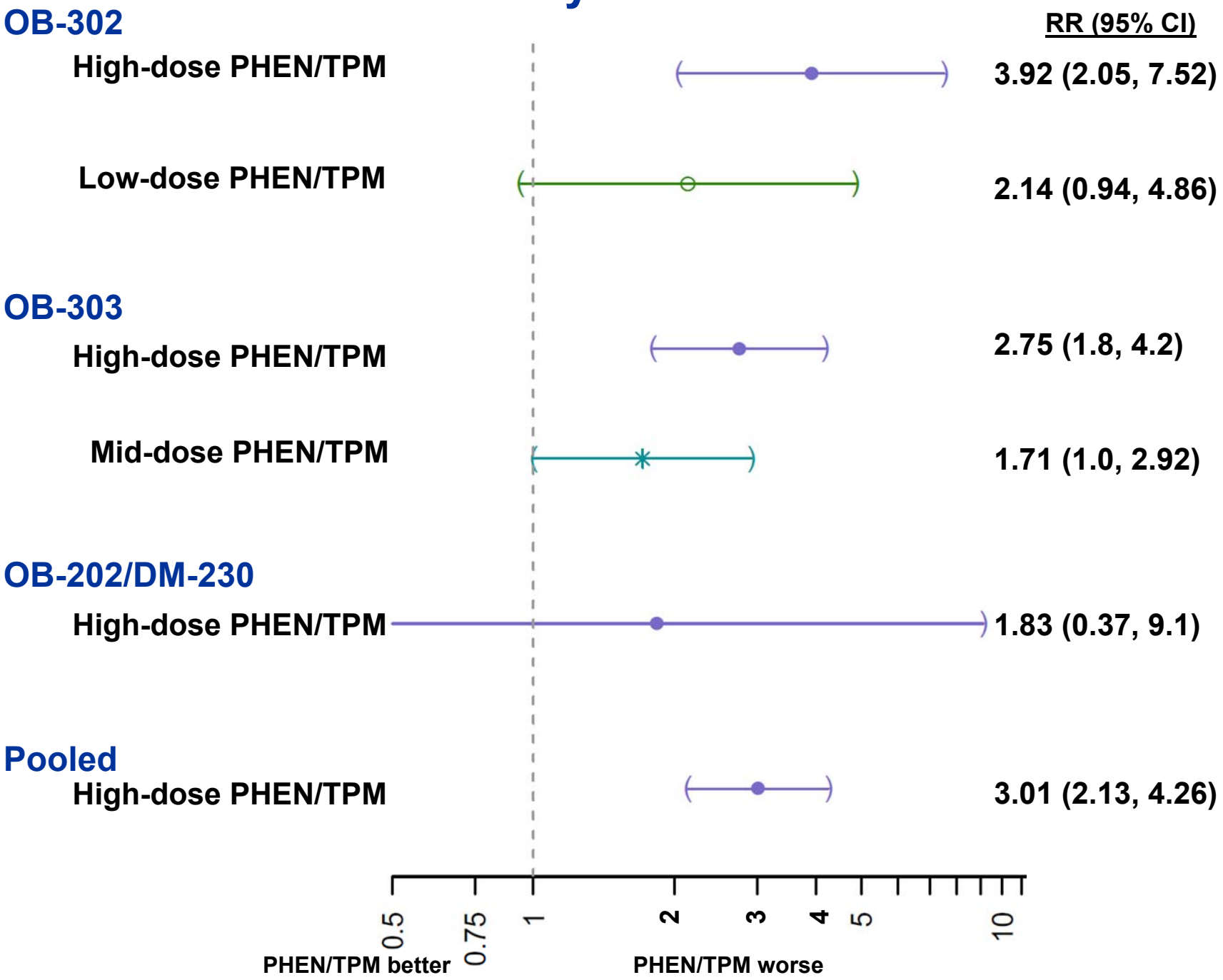
	Placebo N=1561 n (%)	Low-dose PHEN/TPM N=240 n (%)	Mid-dose PHEN/TPM N=498 n (%)	High-dose PHEN/TPM N=1580 n (%)
Psychiatric disorder class	**161 (10.3)**	**38 (15.8)**	**72 (14.5)**	**325 (20.6)**
Sleep disorders	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)
Anxiety	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)
Depression	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)
Suicide/self-injury	1 (0.1)	1 (0.4)	0	0

- Psychiatric adverse events occurred in 20.6% of high-dose PHEN/TPM exposed versus 10.3% placebo exposed
- More individuals treated with PHEN/TPM reported an event in all subclasses aside from suicide/self-injury
- Responsible for 26% of discontinuations associated with adverse events in PHEN/TPM treated individuals vs. 12% of placebo treated individuals
- The proportions of individuals starting psychiatric medications were similar across treatment groups

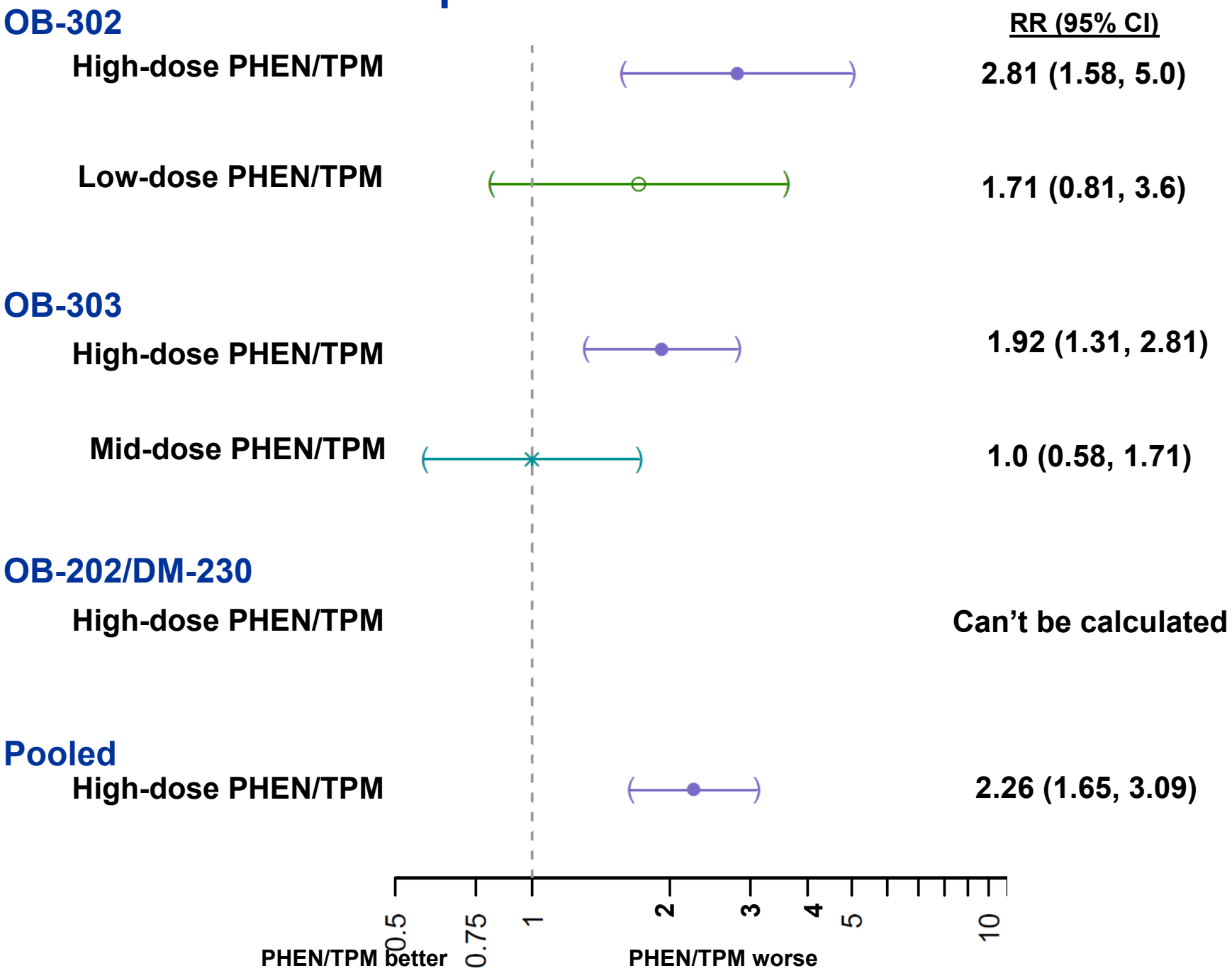
Psychiatric disorders class



Anxiety subclass



Depression subclass

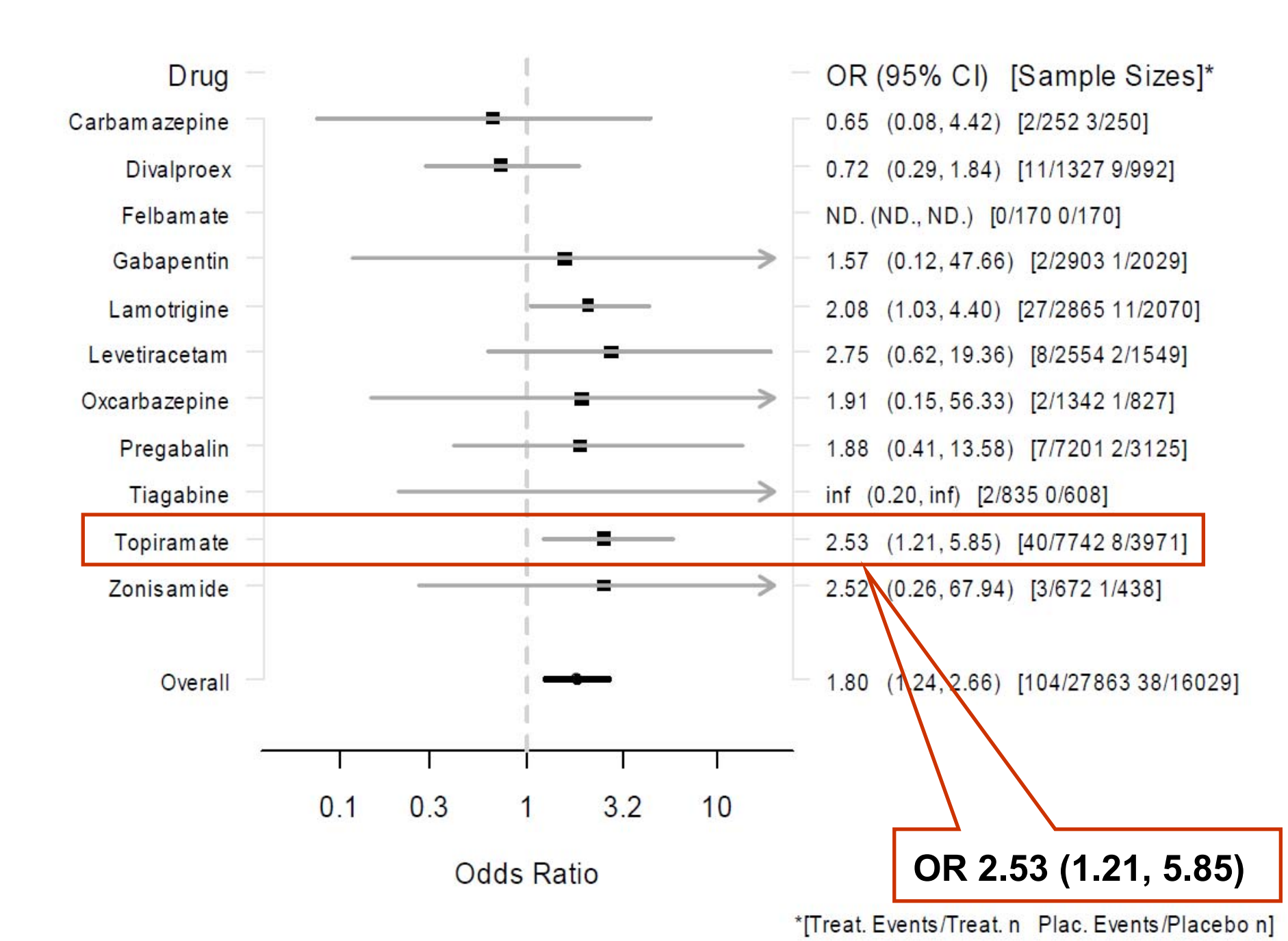


	Subjects with a baseline history of depression			
	Yes N=802		No N=3077	
	Placebo N=334	PHEN/TPM N=468	Placebo N=1227	PHEN/TPM N=1850
Individuals with ≥1 depression-related adverse event	22 (6.6)	48 (10.3)	31 (2.5)	104 (5.6)

- Individuals with a history of depression higher incidence of depression adverse events
- PHEN/TPM treated individuals were more likely to experience a depression-related AE regardless of baseline history of depression

Topiramate and suicidality

- FDA pooled analysis of 199 placebo-controlled trials of 11 different AEDs including topiramate evaluating suicidal ideation/behavior
- Overall adjusted Odds Ratio 1.8 (95% CI 1.2, 2.7)
- Joint meeting of PCNS and PDAC Advisory Committee in July 2008 voted there was a significant risk of suicidality with AEDs, labels must contain this information, medication guide needed, but no box warning


Drug
OR (95% CI) [Sample Sizes]*
Carbamazepine
0.65 (0.08, 4.42) [2/252 3/250]
Divalproex
0.72 (0.29, 1.84) [11/1327 9/992]
Felbamate
ND. (ND., ND.) [0/170 0/170]
Gabapentin
1.57 (0.12, 47.66) [2/2903 1/2029]
Lamotrigine
2.08 (1.03, 4.40) [27/2865 11/2070]
Levetiracetam
2.75 (0.62, 19.36) [8/2554 2/1549]
Oxcarbazepine
1.91 (0.15, 56.33) [2/1342 1/827]
Pregabalin
1.88 (0.41, 13.58) [7/7201 2/3125]
Tiagabine
inf (0.20, inf) [2/835 0/608]
Topiramate
2.53 (1.21, 5.85) [40/7742 8/3971]
Zonisamide
2.52 (0.26, 67.94) [3/672 1/438]
Overall
1.80 (1.24, 2.66) [104/27863 38/16029]
0.1
0.3
1
3.2
10
Odds Ratio
OR 2.53 (1.21, 5.85)
*[Treat. Events/Treat. n Plac. Events/Placebo n]

Suicidality and PHEN/TPM

- Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Tracks suicidal adverse events
  - Administered prospectively
  - Assesses both behavior and ideation and provides a summary measure of suicidality

- There were no suicidal attempts, suicidal behaviors, or instances of serious suicidal ideation recorded by C-SSRS

C-SSRS results	Placebo N=1506 n (%)	Low-dose PHEN/TPM N=240 n (%)	Mid-dose PHEN/TPM N=498 n (%)	High-dose PHEN/TPM N=1505 n (%)
Suicidality (Behavior or Ideation)	**11 (0.7)**	**1 (0.4)**	**3 (0.6)**	**14 (0.9)**
Any suicidal behavior	**0**	**0**	**0**	**0**
Actual attempt	0	0	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	0	0	0	0
Any suicidal ideation	**11 (0.7)**	**1 (0.4)**	**3 (0.6)**	**14 (0.9)**
Wish to be dead	9 (0.6)	1 (0.4)	3 (0.6)	13 (0.9)
Suicidal thoughts	5 (0.3)	1 (0.4)	1 (0.2)	6 (0.4)
Suicidal thoughts with methods	2 (0.1)	0	0	1 (0.1)
Ideation with intent	0	0	0	0
Ideation with plan and intent	0	0	0	0

Adverse events within Suicide/self-injury subclass

- Three episodes of adverse events coded as suicidal ideation
  - one in a placebo treated individual (Day 194)
  - two episodes in PHEN/TPM treated individuals
    - Low-dose (Day 47)
    - High-dose (Day 24)

Conclusions: Psychiatric disorders/PHEN/TPM

- Evidence of increased psychiatric events associated with phentermine and topiramate in previous clinical experience at doses generally higher than PHEN/TPM
- PHQ-9 and C-SSRS showed no imbalances in depression scores and suicidality
- Higher incidence of adverse events associated with sleep disorders, anxiety, and depression with PHEN/TPM treatment compared to placebo

Neurocognitive adverse events

Topiramate and cognition

- Topiramate associated with impaired attention/concentration, memory loss, slowed thinking, and language difficulties at high and low doses (<100 mg/day)
  - Tatum 2001, Lee 2006, Mula 2003, De Ciantis 2008
- Cognitive deficits related to dose and rapid titration
- Hypothesis phentermine co-administration may counteract cognitive slowing

Targeted medical events

- **Cognitive disorders**
  - Attention
  - Language
  - Memory Impairment
  - Other Cognitive NOS

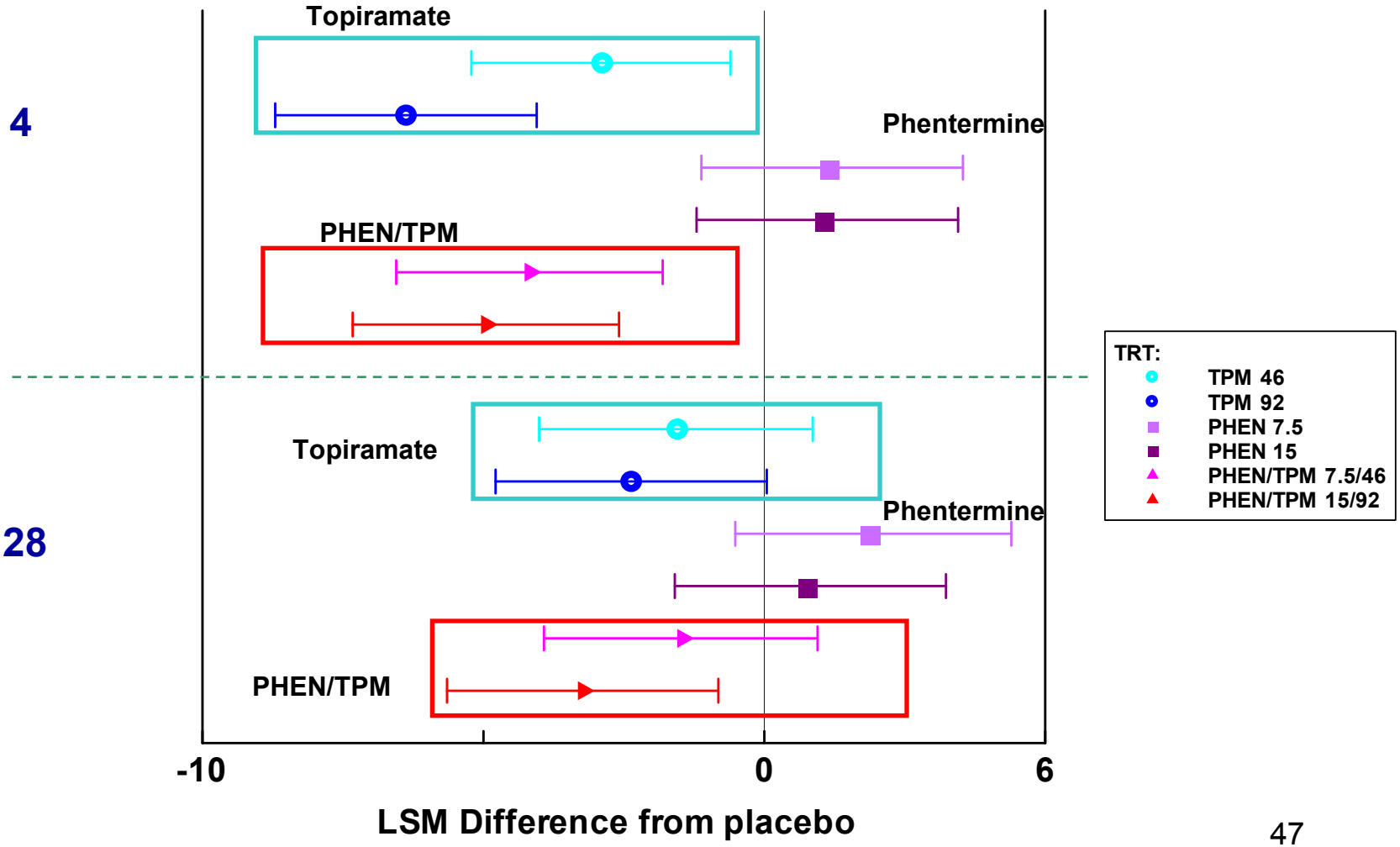
1-YEAR cohort				
	Placebo **N=1561** **n (%)**	**Low-dose PHEN/TPM** **N=240** **n (%)**	**Mid-dose PHEN/TPM** **N=498** **n (%)**	**High-dose PHEN/TPM** **N=1580** **n (%)**
Cognitive disorders	**26 (1.7)**	**5 (2.0)**	**28 (5.6)**	**124 (7.8)**
Attention	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)
Memory impairment	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)
Language	1 (0.1)	0	3 (0.6)	19 (1.2)
Other cognitive disorders	8 (0.5)	2 (0.8)	8 (1.6)	33 (2.1)

- Four times more likely to experience a Cognitive disorder compared to placebo
- Dose-dependent
- All mid- and high-dose PHEN/TPM-treated individuals had a higher frequency of events compared to placebo
- 10% of adverse events leading to discontinuation in PHEN/TPM versus 5% in placebo
- No events categorized as serious

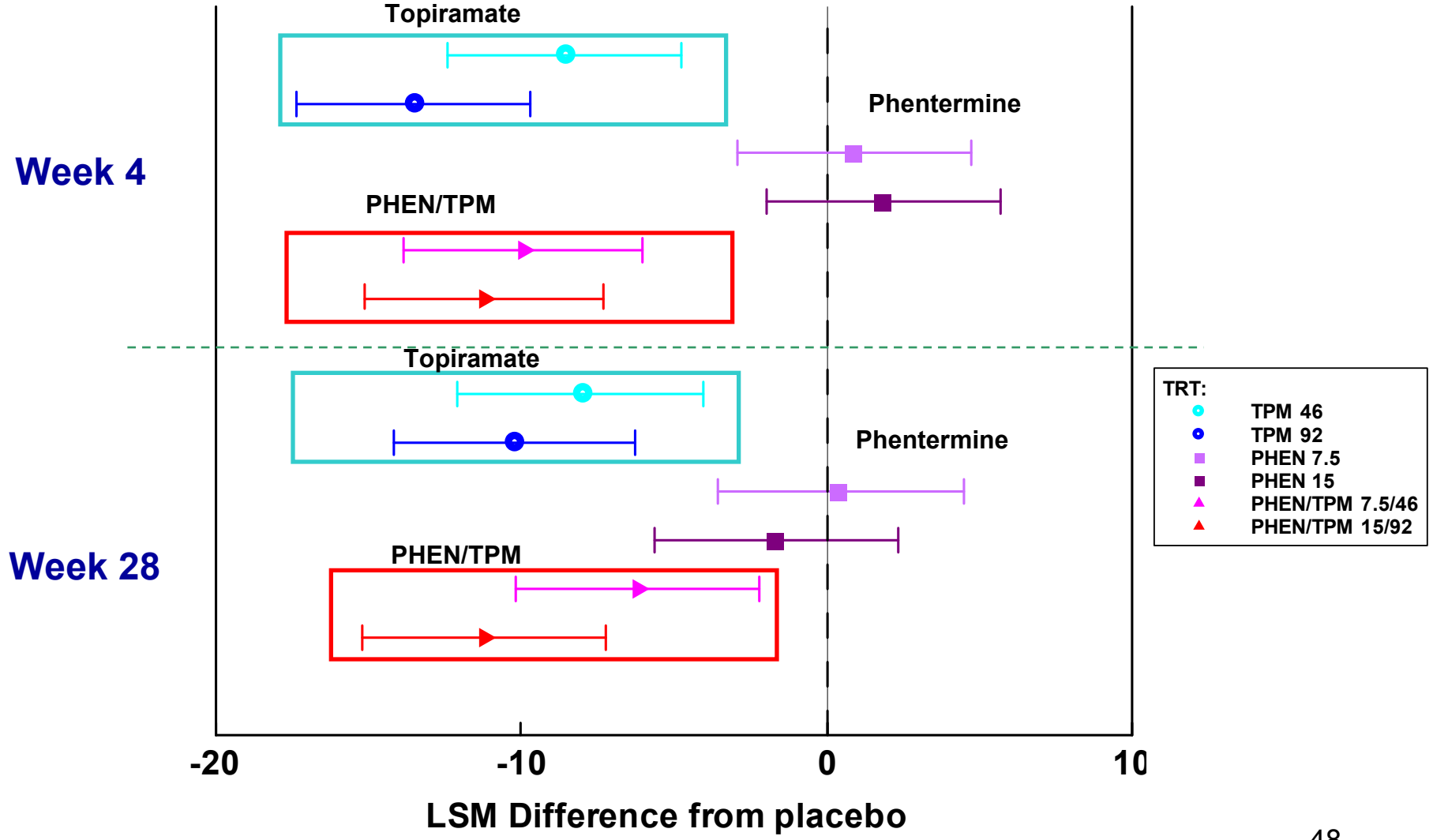
Repeatability Battery for the Assessment of Neuropsychological Status (RBANS)

- Battery of neuropsychological tests
  - 5 cognitive domains
    - Immediate memory
    - Visuospatial/constructional
    - Language
    - Attention
    - Delayed memory
- Done in study OB-301 at Wk 0, Wk 4, and Wk 28 or early termination

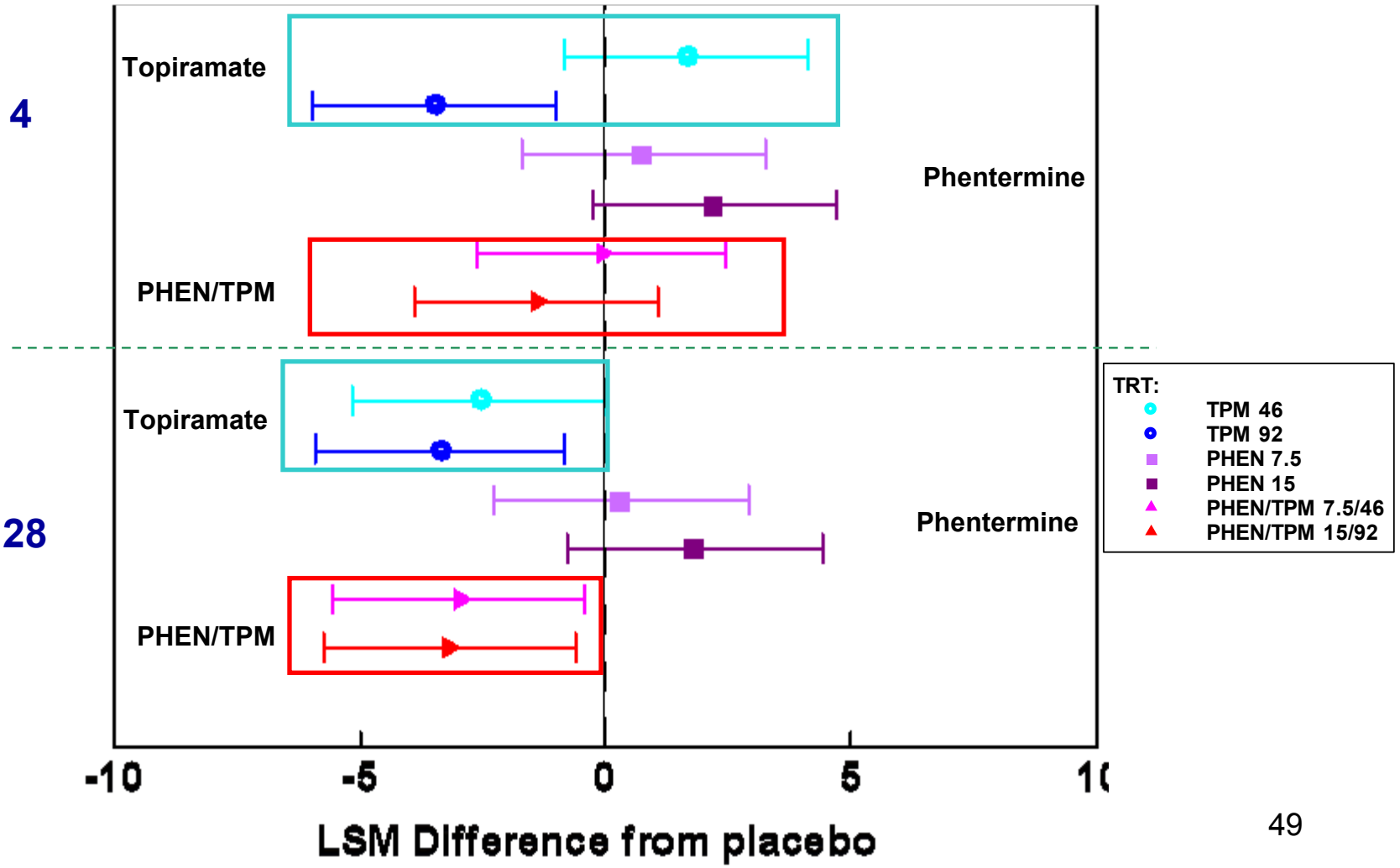
OB-301 RBANS:Total



OB-301 RBANS: Attention



OB-301 RBANS: Language



RBANS cognitive domains

- **Immediate memory:**
  - No effects
- **Visuospatial/Constructional:**
  - No effects
- **Delayed memory:**
  - Week 4: high-dose

Neurocognitive adverse events

- Topiramate effect on cognition well established in individuals with epilepsy and migraines at low and high doses
- PHEN/TPM demonstrated a dose-dependent adverse effect on cognitive disorders in overweight and obese adults
- RBANS testing in obese adults demonstrated topiramate effects were not mitigated by phentermine co-administration

Cardiovascular safety

Phentermine and "fen-phen"

- Phentermine was a component of "fen-phen" linked to increased risk of cardiac valvulopathy
- Fenfluramine and its metabolites agonist activity at $5HT_{2B}$ receptor responsible
- Phentermine does not have significant activity at the $5HT_{2B}$ receptor

Targeted medical events

- **Cardiac disorders**
  - Cardiac arrhythmia
  - Ischemic heart disease

Cardiac disorder class

1-YEAR cohort				
	Placebo N=1561 n (%)	**Low-dose PHEN/TPM N=240 n (%)**	**Mid-dose PHEN/TPM N=498 n (%)**	**High-dose PHEN/TPM N=1580 n (%)**
Cardiac disorder class	**36 (2.3)**	**4 (1.7)**	**24 (4.8)**	**78 (4.9)**
Cardiac arrhythmia	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)
Ischemic heart disease	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)

- Two times more likely to experience adverse event related to cardiac arrhythmia
- Majority were palpitations and tachycardia a known side-effect of phentermine

Heart rate: mean change

1-YEAR cohort				
	Placebo **N=1561** **n (%)**	**Low-dose PHEN/TPM** **N=240** **n (%)**	**Mid-dose PHEN/TPM** **N=498** **n (%)**	**High-dose PHEN/TPM** **N=1580** **n (%)**
Heart rate (bpm)				
Baseline mean (SD)	72.5 (9.58)	72.3 (9.22)	72.2 (10.07)	72.7 (9.87)
Mean change (SD)	0.0 (10.19)	1.3 (10.32)	0.6 (10.18)	1.6 (10.28)

Heart rate: categorical changes

1-YEAR cohort				
	Placebo **N=1561** **n (%)**	**Low-dose PHEN/TPM** **N=240** **n (%)**	**Mid-dose PHEN/TPM** **N=498** **n (%)**	**High-dose PHEN/TPM** **N=1580** **n (%)**
Heart rate				
>5 bpm	1021 (65.4)	168 (70.0)	372 (74.7)	1228 (77.7)
>10 bpm	657 (42.1)	120 (50.0)	251 (50.4)	887 (56.1)
>15 bpm	410 (26.3)	79 (32.9)	165 (33.1)	590 (37.3)
>20 bpm	186 (11.9)	36 (15.0)	67 (13.5)	309 (19.6)

Cardiovascular ischemic events

1-YEAR cohort				
	Placebo N=1561 n (%)	**Low-dose PHEN/TPM N=240 n (%)**	**Mid-dose PHEN/TPM N=498 n (%)**	**High-dose PHEN/TPM N=1580 n (%)**
Cardiac disorder class	**36 (2.3)**	**4 (1.7)**	**24 (4.8)**	**78 (4.9)**
Cardiac arrhythmia	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)
Ischemic heart disease	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)

- 1 cardiovascular death in a placebo treated individual
- Seven placebo treated individuals versus eight PHEN/TPM treated individuals experienced a non-fatal serious cardiac adverse event
  - Placebo: 4 cardiac catherization
  - PHEN/TPM: 5 cardiac catherization
- Cerebral ischemic events
  - Two placebo treated: thalamic infarction, brain stem infarction
  - One high-dose PHEN/TPM treated: acute non-hemorrhagic infarct

Cardiovascular safety

- Palpitations and tachycardia were the most common terms reported in cardiac arrhythmia subclass
- Clinical significance of elevations in heart rate and decrease in blood pressure unknown in the overweight and obese population
- Ischemic events were too few in number to draw any conclusions regarding PHEN/TPM and its effect on major cardiovascular events
- PHEN/TPM cardiovascular outcomes trial proposed

Metabolic acidosis

Metabolic acidosis

- Topiramate's activity as a carbonic anhydrase inhibitor is associated with a hyperchloremic metabolic acidosis

- Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis, osteomalacia or osteoporosis, and affect growth in children

Bicarbonate: mean change

1-YEAR cohort				
	Placebo **N=1561** **n (%)**	**Low-dose PHEN/TPM** **N=240** **n (%)**	**Mid-dose PHEN/TPM** **N=498** **n (%)**	**High-dose PHEN/TPM** **N=1580** **n (%)**
Bicarbonate mEq/L				
Baseline mean (SD)	26.2 (2.52)	26.4 (2.54)	26.1 (2.72)	26.3 (2.49)
Mean change (SD)	0.2 (3.09)	-1.6 (3.01)	-0.3 (3.12)	-1.3 (3.19)

Bicarbonate: categorical change

	Placebo N=1561 n (%)	Low-dose PHEN/TPM N=240 n (%)	Mid-dose PHEN/TPM N=498 n (%)	High-dose PHEN/TPM N=1580 n (%)
Bicarb <21 mEq/L				
Any time post-randomization	92 (5.9)	39 (16.3)	112 (22.5)	474 (30.0)
During Titration Phase	34 (2.2)	18 (7.5)	42 (8.4)	240 (15.2)
During Maintenance Phase	66 (4.2)	31 (12.9)	88 (17.7)	355 (22.5)
Persistence	33 (2.1)	21 (8.8)	32 (6.4)	203 (12.8)
Bicarb <17 mEq/L				
Any time post-randomization	4 (0.3)	4 (1.7)	8 (1.6)	31 (2.0)
During Titration Phase	1 (0.1)	0	3 (0.6)	12 (0.8)
During Maintenance phase	3 (0.2)	4 (1.7)	6 (1.2)	23 (1.5)
Persistence	1 (0.1)	3 (1.3)	1 (0.2)	11 (0.7)

•Numbers reflect subjects on drug
•Persistence defined as two consecutive visits or at final visit

Nephrolithiasis

	Placebo N=1561 n (%)	Low-dose PHEN/TPM N=240 n (%)	Mid-dose PHEN/TPM N=498 n (%)	High-dose PHEN/TPM N=1580 n (%)
Nephrolithiasis	5 (0.3)	1 (0.4)	1 (0.2)	20 (1.3)
Calculus urinary	0	0	0	1 (0.1)

- Two cases of nephrolithiasis and urinary calculus in high-dose group considered serious

Metabolic acidosis

- Imbalances noted in frequency of bicarbonate less than 21 and 17 mEq/L with PHEN/TPM treated compared to placebo

- A large proportion of individuals (30%) treated with high-dose PHEN/TPM had a bicarbonate less than 21 mEq/L

- Long-term effects of PHEN/TPM associated metabolic acidosis on bone and growth unknown

Teratogenicity

Animal studies: topiramate

- Topiramate is a teratogen in several animal species
- Mouse: 2x high dose exposure
  - Craniofacial abnormalities
- Rabbit: 6x high dose exposure
  - Rib and vertebral malformations
- Rat: 34x high dose exposure
  - limb malformations including ectrodactyly, micromelia, and amelia

PHEN/TPM embryofetal studies

- Rabbits: 1x high-dose
  - No teratogenic effect
- Rats: 2x high-dose
  - No teratogenic effect
- Caveats
  - Doses used not associated with teratogenesis
  - Not designed to assess toxicity
  - Designed to evaluate potential additive or synergistic effects on development

Conclusions from animal studies

- No significant drug interaction between topiramate and phentermine resulting in teratogenesis at doses tested
- Does not negate the known teratogenic profile of topiramate in multiple species

Topiramate exposed human pregnancies

- UK Epilepsy and Pregnancy Register
  - 70 topiramate monotherapy exposed pregnancies
  - Three major malformations (4.8%, 95% CI: 1.7, 13.3%)
    - Two oral cleft abnormalities (200 mg/d and 600 mg/d)
    - One hypospadias (400 mg/d)
    - Duration of exposure unknown
    - No control groups

Hunt et al. Neurology 2008

North American AED Pregnancy Registry

- Prevalence of major malformation 3.8% (11/289)
- Relative risk for major malformation with topiramate exposure was 2.8 (95% CI: 1.0-8.1) when compared to controls
- Four infants exposed cleft lip
  - 2 isolated cleft lip (0.69%)
  - Expected prevalence (0.07%)
- Relative risk for low birth weight (<2500g) was 2.7 (95% CI: 1.4-5.1)
- Topiramate monotherapy associated with higher risk of major malformation and low birth weight compared to controls

Hernandez-Diaz et al. Presented at Teratology Society Meeting June 2010

FDA AERS database review

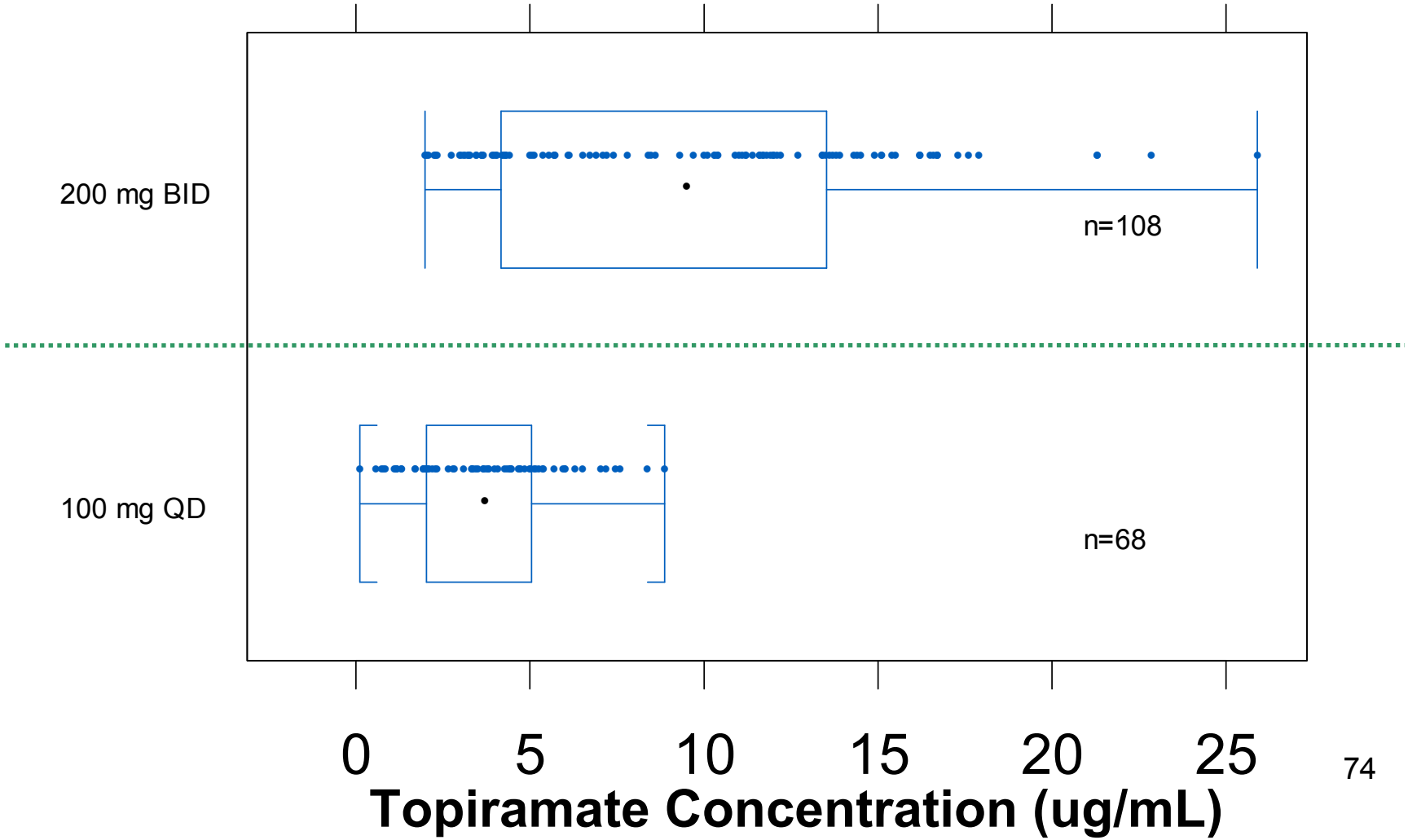
- 64 cases of topiramate exposed pregnancies with malformation reported not related to a genetic condition

Type of malformation	N reported (% of all malformation cases)
Malformations specified	**64**
Craniofacial	**21/64 (32.8%)**
-Cleft lip and/or palate	11
-Facial dysmorphism (incl. auricular dysplasia)	6
-Micrognathia	4
-Skull deformation and ossification abnormalities	3
-Macroglossia	1
Skeletal	**19/64 (29.9%)**
Cardiovascular	**15/64 (23.4%)**

FDA AERS database review

- Of these cases with congenital malformations
  - 88% exposed in 1st trimester
    - 50% did not continue treatment past 1st trimester
  - Adverse events reported at doses ≤200 mg were not different compared to higher doses (>400 mg)

C_{max} values for TPM 100 mg QD and TOPAMAX 200 mg BID



PHEN/TPM and pregnancy

- Participation required:
  - Agreement to use double-barrier or OCP + single barrier
  - Monthly negative urine pregnancy test
- 34 pregnancies during PHEN/TPM clinical development program
  - 19 pregnancies delivered
  - 6 elective terminations
  - 6 spontaneous terminations
  - 1 ectopic
  - 1 unknown
  - 1 lost to follow-up

PHEN/TPM and pregnancy

- Majority occurred in high-dose group
- 13 pregnancies occurred on OCP
- All discontinued drug
- Average gestational age 5.4 weeks at diagnosis
- No anomalies noted

PHEN/TPM interactions with OCP

- Co-administration of multiple once-daily doses of high-dose PHEN/TPM with a single oral contraceptive dose containing 35 µg ethinyl estradiol and 1 mg norethindrone decreased the $AUC_{0\text{-inf}}$ of ethinyl estradiol by 16% and increased the C_{max} and $AUC_{0\text{-inf}}$ of norethindrone by 22% and 16%, respectively

- Unclear how much decrease in hormone concentration will allow pregnancy to occur

- The increase in norethindrone may be in favor of maintaining the contraceptive efficacy

Other considerations

- Higher rates of contraceptive non-use in obese women/adolescents
  - Edelman et al. Contraception 2009
- Risk of venous thromboembolic disease with obesity. Potential higher risk with OCP use
  - Abdollahi et al. Thrombosis & Haemostasis 2003
- Weight loss may increase fertility

Conclusions: teratogenicity

- Repeated pattern of craniofacial congenital malformations
  - Animal studies
  - UK pregnancy registry
  - North American AED pregnancy registry
  - FDA AERS database

- High likelihood of PHEN/TPM exposed pregnancies

PHEN/TPM Benefit: Risk assessment

- **Potential benefits**
  - Significant weight loss
    - 5% weight loss
      - 19.6% placebo
      - 44.9% low-dose
      - 62.1% mid-dose
      - 68.9% high-dose
    - 10% weight loss
      - 7.4% placebo
      - 18.8% low-dose
      - 37.3% mid-dose
      - 47.5% high-dose
  - Improvement in weight-related co-morbidities
- **Potential risks**
  - 1.5-2 times higher risk psychiatric events
  - 4 times higher risk cognitive impairment
  - Increased heart rate
    - >20 bpm
      - 11.9% placebo
      - 15% low-dose
      - 13.5% mid-dose
      - 19.6% high-dose
  - Decreased serum bicarbonate
    - Bicarbonate <21 mEq/L
      - 5.9% placebo
      - 16.3% low-dose
      - 22.5% mid-dose
      - 30% high-dose
  - Possible teratogenicity

Acknowledgments

Medical Review Team
Amy Egan, M.D.
Eric Colman, M.D.

Clinical Pharmacology Team
Johnny Lau, Ph.D.
Justin Earp, Ph.D.
Sally Choe, Ph.D.

Maternal Health Team
Jeanine Best, MSN, RN, PNP
Karen Feibus, M.D.

Project Managers
Pat Madara
Pooja Dharia

Pharmacology/Toxicology
David Carlson, Ph.D.
Todd Bourcier, Ph.D.

Statistical Review Team
Lee Ping Pian, Ph.D.
J. Todd Sahlroot, Ph.D.
Benjamin Neustifter, Ph.D.
Mat Soukup, Ph.D.

Consults
Sonia Tabacova, Ph.D.
Peter Como, Ph.D.
Len Kapcala, M.D.

Charge to the Advisory Committee

1) Taking into account the results of the assessments made with the PHQ-9 and the Columbia Suicidality Severity Rating Scale (C-SSRS), please comment on the significance of the increased adverse event reports of depression, anxiety, and sleep disorders in subjects treated with PHEN/TPM.
   - If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

2) Please comment on the potential significance of the increased adverse event reports of disorders of attention, memory, language, and other cognitive disorders in subjects treated with PHEN/TPM.

- If approved, please discuss need for monitoring and possible monitoring strategies.

3) Please comment on the potential clinical significance of the metabolic acidosis determined by decreases in serum bicarbonate levels with PHEN/TPM treatment.

- If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

4) Please comment on the potential clinical significance of the increase in heart rate observed in PHEN/TPM treated individuals.

- If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

5) Given the doses of topiramate in PHEN/TPM, please comment on whether you believe PHEN/TPM poses a teratogenic risk to the target population for weight loss.

- If you believe it does pose a risk, please comment on how this risk should be managed in women of child-bearing potential if PHEN/TPM is approved.

6) Based on the current available data, do you believe the overall benefit-risk assessment of PHEN/TPM (QNEXA) is favorable to support its approval for the treatment of obesity in individuals with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with weight-related co-morbidities?

Vote: Yes/No/Abstain

If voting yes:

- Please discuss the basis for this recommendation
- Please discuss any labeling recommendations
- Please discuss whether additional studies should be conducted post-approval

If voting no:

- Please discuss basis for this recommendation
- Please discuss what additional studies would be necessary to address an outstanding deficiency/deficiencies